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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,619	10/17/2003	Margot Mary O'Toole	AM100990	9490

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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,619	O'TOOLE ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,8 and 22* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,8,22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/11/2008 has been entered.

2. Currently Claims 1-2, 4-5, 8, and 22 are pending. Claims 3, 6-7, 9-21 have been cancelled. Claim 4 has been withdrawn as being drawn to a nonelected invention.

3. The following rejections to Claims 1-2, 5, 8, and 22 are reiterated. Response to arguments follows.

4. This action is Nonfinal.

Reiterated Rejections

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2, 5, 8, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method of identifying an increased likelihood of lupus nephritis in a mouse, the method comprising the steps of:

a) Obtaining a kidney sample from a control mouse and a mouse of interest

b) Detecting an expression level of the midkine mRNA transcript in the kidney sample of the control mouse and the mouse of interest

c) Comparing the midkine mRNA transcript level of the control mouse and the mouse of interest, wherein an increased expression level of the midkine mRNA transcript level of the mouse of interest relative to the expression level of the midkine mRNA transcript level indicates that the mouse of interest has an increased likelihood of lupus nephritis,.

does not reasonably provide enablement for methods to diagnose lupus nephritis (LN) in human by detecting an elevated expression level of midkine gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims

The claims are broadly drawn to diagnosing lupus nephritis in a human or a mouse comprising detecting the expression level of midkine gene in a kidney sample wherein an elevated expression level indicates an increased likelihood of lupus nephritis. The claims are broadly drawn to include methods where both human and mouse are subjects.

The invention is in a class of inventions that the CAFC has characterized as "the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification

The specification teaches systematic lupus erythematosus (SLE) is an autoimmune disease that has diverse and variable clinical manifestations that range from skin rash and joint pain that can show spontaneous remissions to severe kidney disease that may result in renal failure, otherwise known as lupus nephritis (LN). Midkine (MDK) has several functions including neural-glial interactions in brain development, inflammation, tumor and angiogenesis, and anti-apoptotic activities (specification, pages 14-19). The specification asserts that midkine is a marker for SLE or LN, and its expression can be utilized as a diagnostic for said diseases (page 4). The specification concludes "MDK has not previously been associated with SLE and LN....While mouse models were used for the initial differentiation expression analysis; it is well-appreciated that animal

models can be interpreted to reflect expression levels from human subjects as well. The present invention…encompasses human MDK" (page 22). The specification further asserts "without limitation as to mechanism, the present invention is based in part on the principle that modulation of the expression of the MDK gene expression may ameliorate SLE/LN, when they are expressed at levels similar or substantially similar to normal non-diseased tissues" (page 23).

The specification discloses working examples of the isolation of RNA from kidney samples of several different mouse models of lupus that ranged in age of five months to 8, 16, 20 weeks of age, thus representing early, intermediate, and late stages of lupus, and control mice of the same age range. The working examples disclose that after the isolation of kidney tissues from said mice, RNA was isolated and cDNA was synthesized, and then the samples were analyzed with Affymetrix Mu11KsubA and Mu11KsubB microarrays. Statistical analysis was subsequently performed, and TaqMan assays were performed on genes of interest (pages 13-14 and 78-82).

State of the Prior Art

Kotzin et al. teaches (Cell, 1996, Vol. 85, pages 303-306) the underlying cause of lupus has yet to be determined as environmental factors such as sun exposure, viral or bacterial infections, hormonal and drug treatments, and genetic contributions play a role in the manifestation of the disease (Kotzin, page 305). Kotzin teaches several animal models have been used to study lupus, however, due to the complex nature of the disease, "even when one animal model and one phenotype is considered, the genetic basis of lupus-like disease is remarkably complex, involving contributions from multiple

genes in addition to class II MHC....Furthermore, it seems likely that different genetic contributions are operative in different animal models (and therefore in different patients), even when the same phenotype is being followed" (page 305). Kotzin further teaches mouse models are used to study the genetic causes of lupus, and to predict human genes that are associated with said disease since mouse and human genes are homologous (Journal of Clinical Investigation, 1997, Vol.99, No. 4, pages 557-558). However, as stated above, environmental factors and phenotypic expression of lupus have considerable variation, and since the environment conditions are controlled for animal studies and the animal models are bred to have uniform lupus symptoms, it is unclear if results from animal studies can be applicable to humans. Kotzin teaches, "disease phenotype among mice in each cross is much more uniform compared to the relatively heterogeneous disease expression in patients. Especially in SLE, clinical manifestations and autoantibody production can be extremely diverse and variable, which is in part genetically based, and this variability can confound genetic studies" (Journal of Clinical Investigation, page 557). To ensure accurate predictions of the results of mouse lupus models to humans "there should also be concern that an initial mapping in a complex trait reflects false positive readings....If true, this human locus...may not be in a region synthenic to the murine susceptibility locus, and linkage in the current human study would therefore represent quite a fortuitous finding," and in order to ensure accurate results, large studies of human patients will need to be performed (Kotzin, Journal of Clinical Investigation, page 558).

The Relative Skill of Those in the Art

The level of skill in the art is deemed to be high.

The Predictability or Unpredictability of the Art and Degree of Experimentation

Moreover, as indicated by Kotzin et al., an animal model may not be an accurate representation of another animal's response to lupus. Genetic homology does not necessarily correlate to phenotypic expression. As mentioned previously, environmental factors play a role in the development of lupus, and it is unpredictable if a mouse, particularly in a controlled environment, will react in the same manner to environmental factors as humans.

Liu et al. (Clinical Immunology 2004 Vol. 112 p. 225) teaches that that correlation of genes to disease traits in mouse models is not indicative of correlation in humans. Liu et al. teaches that the gene expression profile of humans with autoimmune disease is not the same as the gene expression in a mouse model and in fact there is very little overlap in the gene expression profile of the two (Abstract). Liu et al. found that there was no overlap between the differentially expressed genes between human and mouse data sets with regard to systemic lupus (p. 228 1st column 1st paragraph). Liu et al. teaches that their results show that murine models do not perfectly model corresponding human autoimmune diseases when gene expression profiles are considered (p. 229 2nd column last paragraph).

Morel et al. (PLOS Biology August 2004 Vol. 2 p. 1061) teaches that one cannot directly apply data obtained from animal models to human diseases (p. 1062 1st column

last paragraph). Morel et al. teaches that human autoimmune diseases (which includes lupus) show extremely heterogeneous clinical presentation and that animal models only present a simplified version (p. 1062 1st column last paragraph). Morel et al. teaches the mouse model only provides a partial representation of the real biological complexity underlying the human disease (p. 1062 1st column last paragraph). Morel et al. teaches that extrapolation from animal models to autoimmune patients are limited by the differences between the two immune systems (p. 1062 2nd column 1st paragraph).

Consequently, it is unpredictable if a mouse phenotypic expression of lupus will be similar to humans. Consequently, the skilled artisan would have to examine midkine's expression in As a result, the specification does not teach the person skilled in the art how to reasonably predict, without undue burden, SLE or LN by midkine expression levels in a biological sample of human.

Enard et al. (Science 2002 Vol 296 p. 340) teaches that even between closely related species gene expression patterns differ (abstract). Enard et al. teaches that mRNA expression levels are different between humans, chimpanzees, orangutans and rhesus marcques (p. 340 1st column last sentence-2nd column 1st paragraph). Enard et al. teaches that there are a large number of quantitative differences in gene expression in closely related mammals (p. 342 2nd column last paragraph). Therefore the art teaches that even between very closely related mammals there is a divergence of gene expression.

Amount of Direction or Guidance Provided by the Specification

Though the specification provides working examples of mouse models with regard to the detection and correlation of elevated expression levels of midkine gene, the specification has not provided sufficient guidance to extrapolate these results to human. Further the art teaches that correlations in mouse models are not sufficient to correlate expression in humans. The art also teaches that expression profiles of genes differ in humans afflicted with autoimmune disease and mouse models with autoimmune disease. Therefore the specification has not provides sufficient guidance to one skilled in the art to correlate elevated midkine levels to lupus in humans. Further the skilled artisan would have to perform undue experimentation to correlate midkine levels with lupus in humans because the art teaches that correlations in mouse models cannot be extrapolated to humans without intervening experimental steps, which have no guarantee of success.

Working Example

The specification does not provide working examples of methods to diagnose lupus with midkine expression levels in human. The methods do not demonstrate the methodology can be used to predictably diagnose lupus with midkine mRNA in humans.

Conclusions

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re

Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in Genentech Inc. v Novo Nordisk 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In view of the high level of unpredictability in the art and lack of guidance provided by the specification and prior art, undue experimentation would be required to practice the claimed invention.

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is presented below with response to arguments following.

(A) The reply asserts that without regard to the teachings of the specification and the 1.132 declaration submitted on 10/23/2007, the claims are rejected under 35 USC 112 (p. 2 3rd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

It is noted that the final rejection (1/11/2008) fully responded to all arguments and points discussed in the 1.132 declaration, however, the points raised by the 1.132 declaration did not overcome the lack of enablement presented in the final rejection of

1/11/2008 under 35 USC 112/Scope of Enablement. The reply has not pointed to any specific arguments which were not addressed concerning the CFR 1.132 declaration.

(B) The reply asserts that the office action uses an incorrect assertion of the teachings of Liu et al. to conclude that there is unpredictability in extrapolating the mouse model to humans (p. 2 4th paragraph). The reply asserts that instant of showing unpredictable findings between the mouse model to humans (p. 2 4th paragraph), it instead found two overlapping differentially expressed genes between humans with SLE and mice (5th paragraph p. 2).

These arguments have been fully reviewed but have not been found persuasive.

The reply asserts that the teachings of Liu et al. shows the predictability of the association of gene expression of lupus in mouse as extrapolated to humans and argues that there is not unpredictability in the teaching.

Liu et al. teaches that the gene expression profile of humans with autoimmune disease is not the same as the gene expression in a mouse model and in fact there is very little overlap in the gene expression profile of the two (Abstract). Liu et al. found that there was no overlap between the differentially expressed genes between human and mouse data sets with regard to autoimmune diseases (p. 228 1st column 1st paragraph). Liu et al. teaches that their results show that murine models do not perfectly model corresponding human autoimmune diseases when gene expression profiles are considered (p. 229 2nd column last paragraph). The reply seems to be asserting that there is overlap with regard to differently expressed genes in the case of

SLE taught in Liu (figure 2 of Liu). However, though there is some over lap, namely two gees p27 and cadherin11, the expression provides do not completely overlap. In the instant case out of the 129 genes tested only 2 overlap between human and mouse. Which indicates that it is not predictable that any gene expression observed in a mouse model can be extrapolated to a human subject, but rather, each gene expression must be individually tested and correlated without a reasonable expectation of success.

(C) The reply asserts that based upon the teaching in the specification and the art that it would be enabling to identify the increased likelihood of lupus nephritis in a human by comparing the midkine mRNA expression level in the kidney of the human with that of a control human (p. 3 2nd paragraph). The reply asserts that the instant specification discloses that over expression of midkine contributes to protection from cell death and induces phosphorylation of Akt in human tissues (p. 3 3rd paragraph). The reply asserts that Akt1 has an upstream role in mTOR pathway (p. 3 3rd paragraph). The reply asserts a statistical test of the overlap of the mTOR pathway with genes published in literature for human lupus indicates that proteins that interact with mTOR pathway show an association with human lupus (p. 3 3rd paragraph). The reply asserts that that rapamycin which is an mTOR inhibitor has been used to treat patients with SLE (p. 3 3rd paragraph). The reply asserts that the specification describes restoration of midkine expression to normal levels after administration of rapamycin in mice (p 3 3rd paragraph

These arguments have been fully reviewed but have not been found persuasive.

The reply is asserting that because protein expression of midkine is associated with the treatment of SLE in patients, that it would be predictable to extrapolate mRNA expression level findings in a mouse model to a human to predict a increased likelihood of lupus in a human.

The reply asserts that mTOR pathway has been associated with human lupus, however, the reply does not point to any reference or description in the specification that supports such an assertion and therefore the Attorney's arguments cannot take the place of evidence on the record. As stated in the MPEP, 2106 "Arguments of Counsel"

"However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See In re Budnick, 537 F.2d at 538, 190 USPQ at 424; In re Schulze, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); In re Cole, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement."

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.
Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:
(1) prior to a final rejection,
(2) before appeal in an application not having a final rejection, or
(3) after final rejection and submitted
(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
(iii) under 37 CFR 1.129(a).

However, in response to the assertion that protein expression of midkine is associated with the treatment of SLE in patients, that it would be predictable to extrapolate mRNA expression level findings in a mouse model to a human to predict a increased likelihood of lupus in a human. Enard et al. (science 2002) teaches that there are differences in mRNA expression levels between closely related species (abstract). Enard et al. teaches that similarities or differences in mRNA levels are not necessarily translated into differences or similarities in protein levels (p. 342 1st full paragraph). Therefore though a midkine repressor drug treats lupus, it does not provide support that increase midkine mRNA expression is correlative to lupus because the art teaches that the mouse model expression data is not extrapolated to human without undue experimentation.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
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